

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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| <p>(51) International Patent Classification⁴ : A61K 9/16, 9/50, 47/00</p> | <p>A3</p> | <p>(11) International Publication Number: WO 88/ 07365 (43) International Publication Date: 6 October 1988 (06.10.88)</p> |
| <p>(21) International Application Number: PCT/US88/01096 (22) International Filing Date: 30 March 1988 (30.03.88) (31) Priority Application Number: 033,432 (32) Priority Date: 1 April 1987 (01.04.87) (33) Priority Country: US (60) Parent Application or Grant (63) Related by Continuation US 033,432 (CIP) Filed on 1 April 1987 (01.04.87) (71)(72) Applicant and Inventor: RANNEY, David, F. [US/US]; 3539 Courtdale Drive, Dallas, TX 75234 (US).</p> | <p>(74) Agent: HODGINS, Daniel, S.; Arnold, White & Durkee, P.O. Box 4433, Houston, TX 77210 (US). (81) Designated States: AT, AT (European patent), AU, BB, BE (European patent), BG, BJ (OAPI patent), BR, CF (OAPI patent), CG (OAPI patent), CH, CH (European patent), CM (OAPI patent), DE, DE (European patent), DK, FI, FR (European patent), GA (OAPI patent), GB, GB (European patent), HU, IT (European patent), JP, KP, KR, LK, LU, LU (European patent), MC, MG, ML (OAPI patent), MR (OAPI patent), MW, NL, NL (European patent), NO, RO, SD, SE, SE (European patent), SN (OAPI patent), SU, TD (OAPI patent), TG (OAPI patent), US. Published <i>With international search report</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i> (88) Date of publication of the international search report: 17 November 1988 (17.11.88)</p> | |

(54) Title: **BIODADHESION DRUG CARRIERS FOR ENDOTHELIAL AND EPITHELIAL UPTAKE AND LESIONAL LOCALIZATION OF THERAPEUTIC AND DIAGNOSTIC AGENTS**



(57) Abstract

This application describes the preparation and in vivo testing of surface coatings and matrix materials, which when applied to or caused to comprise the carriers for drugs and diagnostic agents, and administered in a fashion that allows efficient vascular access, causes the carriers to recognize determinants present on normal or focally diseased endothelium, and induces the following in vivo effects: (1) rapid, partial or total endothelial envelopment of the drug (diagnostic) carrier; (2) sequestration of the carrier and protection of the entrapped agent from blood vascular clearance at an early time (2 minutes) when the endothelial pocket which envelops the carrier still invaginates into the vascular compartment; (3) acceleration of the carrier's transport across and/or through the vascular endothelium or subendothelial structures into the tissue compartment (interstitium); and (4) improvement of the efficiency with which the drug (or diagnostic) carrier migrates across the endothelium, or epi-endothelial or subendothelial barriers, such that a lower total drug dose is required to obtain the desired effect relative to that required for standard agents. Analogous tissue uptake is described for transepithelial migration into the lungs, bladder and bowel.

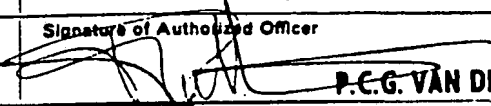
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INTERNATIONAL SEARCH REPORT

International Application No **PCT/US 88/01096**

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| I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) ⁴ | | |
| According to International Patent Classification (IPC) or to both National Classification and IPC | | |
| IPC ⁴ : A 61 K 9/16; A 61 K 9/50; A 61 K 47/00 | | |
| II. FIELDS SEARCHED | | |
| Minimum Documentation Searched ⁷ | | |
| Classification System | Classification Symbols | |
| IPC ⁴ | A 61 K | |
| Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁸ | | |
| | | |
| III. DOCUMENTS CONSIDERED TO BE RELEVANT ⁹ | | |
| Category ⁶ | Citation of Document, ¹¹ with Indication, where appropriate, of the relevant passages ¹² | Relevant to Claim No. ¹³ |
| X | CA, A, 1168150 (ALBERTA UNIVERSITY) 29 May 1984, see claims 1-6,15; page 4, lines 14-20 -- | 1,4,7,37,38, 106 |
| X,Y | EP, A, 0087786 (YEDA) 7 September 1983, see claims 1,6,16,17; page 4, lines 14-22 -- | 1,4,7,9,18, 19,30,34, 37-39,42, 53-56,73, 85-89,102, 112 |
| Y | EP, A, 0167825 (RENTSCHLER) 15 January 1986, see the whole document, in particular claims 1,13 -- | 1,2,4,7, 37-39,42, 106 |
| Y | GB, A, 1516348 (VICTORIA) 5 July 1978, see the whole document, in particular claims 1-5 -- | 1,2,4,18,19, 53-56,73, 85-89,106 |
| Y | GB, A, 2041517 (FUJI) 10 September 1980, see see claims 1,6-9,11,13; page 1, lines 7-9,48-51; page 3, lines 30,31,38,39 -- | 1,4,37,38, 73,112 |
| P,X | EP, A, 0240424 (RENNES UNIVERSITY) ./. | 1,2,4,37,38, 73,112 |
| <p>¹⁰ Special categories of cited documents:</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the International filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"A" document member of the same patent family</p> | | |
| IV. CERTIFICATION | | |
| Date of the Actual Completion of the International Search | Date of Mailing of this International Search Report | |
| 22nd September 1988 | 14 OCT 1988 | |
| International Searching Authority | Signature of Authorized Officer | |
| EUROPEAN PATENT OFFICE |  P.C.G. VAN DER PUTTEN | |

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

| Category * | Citation of Document, with indication, where appropriate, of the relevant passages | Relevant to Claim No |
|------------|---|-----------------------------------|
| P,X | 7 October 1987, see claims 1,10,11, 13,14; page 5, lines 9-11,24-26 --- GB, A, 2185397 (COSMAS-DAMIAN) 22 July 1987, see page 1, lines 37-42; page 6, lines 44-49,54-58; page 7, lines 2,3 ----- | 1,4,7,21, 37-39,73, 106,107 |

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE ¹

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. Claim numbers*..... because they relate to subject matter not required to be searched by this Authority, namely:

*48-51, 118-132, 137-139

See PCT Rule 39.1(iv): Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.

2. Claim numbers*..... because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

* Claims searched incompletely: 1,31,62

Obscure wording (Art. 17.2(a)(ii) PCT) as far as the expression "at least two molecules of drug... contained by the carrier" is concerned.

3. Claim numbers....., because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING ²

This international Searching Authority found multiple inventions in this international application as follows:

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

The additional search fees were accompanied by applicant's protest.

No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO.

US 8801096
SA 21942

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on 07/10/88
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| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|--|------------------|--|--|
| CA-A- 1168150 | 29-05-84 | None | |
| EP-A- 0087786 | 07-09-83 | JP-A- 59051938 US-A- 4732811 | 26-03-84 22-03-88 |
| EP-A- 0167825 | 15-01-86 | DE-A- 3421468 JP-A- 61056122 | 19-12-85 20-03-86 |
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| EP-A- 0240424 | 07-10-87 | FR-A, B 2596399 | 02-10-87 |
| GB-A- 2185397 | 22-07-87 | DE-A- 3700911 | 23-07-87 |

EPO FORM P0179

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82